REMARKS

Applicants have reviewed the Office Action mailed January 25, 2007 (the "Office Action") and have considered the grounds of rejection presented therein. Applicants thank the Examiner for removing the rejections of record over various cited references. Applicants' remarks responsive to outstanding rejections of record can be found *infra* and are believed to fully address all outstanding rejections in full.

List of References Cited

Applicants reiterate their request, made in Applicants' Amendment and Response mailed September 27, 2006 (page 22) for reference Sansom, *Biophys. J.*, 68:1295-1310, (1995), to be made of record in the file history of the instant application. Reference Sansom was cited by the Examiner in the Office Action dated March 27, 2006, but did not appear on an Examiner's PTO-892 form ("Notice of References Cited") at that time.

As set forth in MPEP § 707.05(c) "[i]n citing references for the first time, the identifying data of the citation should be placed on form PTO-892 'Notice of References Cited,' a copy of which will be attached to the Office action." Accordingly, Applicants respectfully request the Examiner's compliance therewith.

Dates of Receipt of various items of Applicants' Correspondence with the Office

Applicants point out to the Examiner that, in their submission of September 27, 2006, a request was made ("Communication to Request Correction of PTO Records") to have PTO records (PAIR) updated to reflect the correct receipt date by the Office of Applicants' response to restriction requirement mailed December 26, 2002. This request has not yet been acted on by the Office. The Examiner's attention thereto is respectfully requested.

Applicants additionally point out that both the aforementioned Communication and Applicants' Response to the March 27, 2006 Office Action were timely filed with the PTO by Express Mail on September 27, 2006. At the request of the Examiner, those items were resubmitted electronically by Applicants on November 2, 2006 because, according to the

Examiner, although the PTO had charged Applicants' deposit account for the applicable extension fee, the various papers submitted had not been entered into the PTO's Image File Wrapper. The PTO's records on PAIR reflect only a November 2, 2006 date of receipt for the materials. Applicants respectfully request the Examiner update the PTO's records to show that the items resubmitted on November 2, 2006 were originally filed timely on September 27, 2006.

Amendments to the Claims

Claims 1, 3, and 35 – 57 and 59-64 are pending in the instant Application. With the instant amendments, Applicants cancel claim 36, and amend claims 1, 35, 46, 47, 49, and 60.

Claim 1 is amended to recite a G-protein coupled receptor in place of the term "membrane-bound protein", such limitation originally found in claim 36 now cancelled herewith.

Claim 1 is also amended to reintroduce an "outputting" step, found at least in claim 1 as originally filed, and to render internally consistent references to a "helix bundle configuration." A lipid bilayer is introduced into the first optimizing step, as found, *e.g.*, in the specification as filed at page 8, ¶ [0016].

Claims 35 and 46, 47, and 60 are amended, correspondingly, to maintain proper antecedent basis for various terms recited therein.

Claim 49 is amended to recite a capitalized form for "Cartesian", consistent with typical scientific notation, and as presented in the specification as filed at ¶ [0033].

Accordingly, no new matter is introduced by way of the amendments herein, and entry thereof is respectfully requested.

Applicants reserve the right to prosecute at least the subject matter deleted from claim 1 in one or more continuation, divisional, or continuation-in-part filings.

REJECTIONS OF THE CLAIMS

Rejections under 35 U.S.C. § 101

The Examiner has rejected claims 1, 3, 35 – 57, 59, 60, and 64 under 35 U.S.C. § 101 for allegedly being drawn to non-statutory subject matter. Notwithstanding Applicants' continued disagreement with the Examiner's line of reasoning that "providing" a predicted protein structure

is insufficient to render the claim statutory without an explicit recitation that the result "provided" is actually "communicated to a user", and in an effort purely to advance prosecution, Applicants hereby amend instant claim 1 to recite "outputting". Applicants believe that this form of amendment should moot the rejection, and remind the Examiner that claim 1 as originally filed recited "outputting" and did not fall prey to a rejection under 35 U.S.C. § 101 based on the reasoning of the instant rejection, or any other reasoning related to allegations of non-statutory subject matter.

That having been said, Applicants understand that, in this instance, the Examincr is constrained not by the law but by recent examination guidelines promulgatcd within the U.S. PTO. Applicants therefore note, for the record, that they do not concede that an act of "outputting" the result – as if to a user – is a pre-requisite to patentability. It is recalled that, under the facts of *State Street Bank* (cited in Applicants' response, September 27, 2006) there was no analogous outputting step and neither did the court's opinion state that one should have been present, and thus the law does not require one to be present to ensure patentability of a claim.

Accordingly, Applicants believe that the instant amendments fully address the rejection of the claims under 35 U.S.C. § 101, and respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 112 (¶ 2)

The Examiner has rejected claims 1, 3, 35 – 57, and 59 – 64, under 35 U.S.C. § 112 (second paragraph) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states, as follows:

> Claim 1, as amended recites the limitation 'to provide a predicted structure.' It is not clear whether 'providing' [*sic*] is intended to be an active, positive method step or merely an intended result of the method.

Applicants believe that the amendment herein, wherein "to provide" is replaced with "outputting", as required by the Examiner in her assessment of patentability under 35 U.S.C. §

101, disposes of the rejection as it stands. Accordingly, Applicants respectfully request removal of the rejection.

Nevertheless, Applicants remain unclear as to the basis of the rejection since, in a previous amendment "thereby providing" resulted in a rejection under the same paragraph of the patent statutes, for essentially the same reason. Since it is well-established practice in claim drafting to recite, in a final step in a process or method, an outcome that ties in with the preamble of the claimed process or method, Applicants request more expansive clarification from the Examiner as to the basis of this rejection were she to maintain it, particularly in light of the amendments herein.

Rejections under 35 U.S.C. § 112 (¶ 1, written description)

The Examiner has rejected claims 1, 3, 35 – 57, and 59 – 64, under 35 U.S.C. § 112 (first paragraph) as allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection based on the amendments herein.

Specifically, the Examiner asserts that "optimizing a helix bundle configuration" is not equivalent to "optimizing [a] configuration of the helix bundle." Applicants take no position on the merits of this distinction, but, instead, draw her attention to amendments to claim 1, and corresponding amendments to claims 35 and 46 that, Applicants believe, address the substance of the Examiner's rejection.

Specifically, claims 1, 35, and 46 now recite the term "helix bundle configuration", and the "optimizing" referenced by the Examiner is carried out "with a lipid bilayer".

Accordingly, Applicants believe that the claims as amended herein comply with the written description requirements of 35 U.S.C. § 112 (first paragraph) and respectfully request that the rejection of record be withdrawn.

Rejections under 35 U.S.C. § 112 (¶ 1, enablement)

The Examiner has rejected claims 1, 3, 35 – 57, and 59 – 64 under 35 U.S.C. § 112 (first paragraph) as allegedly being based on a non-enabling disclosure. Applicants respectfully traverse the rejection based at least on amendments presented herein.

Applicants understand the essence of the Examiner's rejection to be that "the specification, while being enabling for providing a structure of G-protein coupled receptors, does not reasonably provide enablement for ALL membrane spanning proteins." (January 25, 2007 Office Action, at page 5; emphasis therein.) Applicants have herein amended claim 1 to recite "G-Protein coupled receptor" — that class of proteins considered enabled by the Examiner — in place of "membrane-bound protein" and, accordingly, respectfully request that the rejection be withdrawn.

For the record, Applicants state that this amendment is made purely for the purposes of advancing prosecution and do not otherwise agree with the Examiner's position and her characterization of supporting literature references for at least the following reasons.

In the first instance, Applicants point out that the claims prior to amendment herein did not recite "ALL" membrane spanning proteins but just those that comprise a plurality of α-helices. Accordingly Applicants' methods could be reasonably applied to any membrane spanning proteins that comprise a plurality of α-helices because the way in which the steps are carried out is independent of the identity of the protein to which the methods are applied. This remains as true for the G-protein coupled receptors as recited in the instant claims, as for membrane spanning proteins generally.

The Examiner considered eight factors germane to her rejection, as set forth in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).[1] In particular, Applicants consider those factors where they remain in disagreement with the Examiner's characterization where such disagreement may not be mooted by the amendments herein.

First, regarding the alleged breadth of the claims ("factor a"), the Examiner considers that the specification "fails to guide one skilled in the art how to predict a structure of any membrane-spanning protein without knowing how helices interact with a membrane and each other, how they fit into a bundle". In response, Applicants note that the Examiner's assumption that one

[1] Applicants note that the Examiner cites language from *In re Wands* stating that "although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable". The relevance of characteristics of molecular biology is unclear to Applicants, where the instant claims recite methods of protein structure prediction.

skilled in the art must know *a priori* "how helices interact with a membrane and each other, how they fit into a bundle" overlooks the fact that Applicants' claimed method actually determines those very interactions and arrangements (*e.g.*, claim 1 (as amended herein), recites steps of "assembling the optimized structures of the two or more helices into a helix bundle configuration" and "optimizing the helix bundle configuration with a lipid bilayer"). Thus, the supposed requirement to know such information in advance of practicing the claimed methods finds no basis in the manner in which such methods are actually practiced.

Regarding "factors c, and e" the Examiner asserts that, according to three literature references, "modeling proteins is very complicated and has a high degree of uncertainty". Applicants respectfully disagree that the cited references are germane to the instant claims and address each one in turn.

First, the Examiner cites from the Abstract and Introduction of Ginalski, *et al.*, *Nucleic Acids Research*, 33:1874-1891, (2005) (hereinafter, "Ginalski") to suggest that deducing protein structure from sequence is far from an achieved goal. Such a generalization is neither reasonable from a reading of Ginalski nor pertinent to Applicants' claimed invention, which predicts structures for G-Protein coupled receptors. The conclusions from Ginalski are limited to particular classes of methods, and particular types of proteins. Those methods are described at pages 1875 – 1881 of Ginalski and include: "sequence similarity-based", "threading", "hybrid" (sequence similarity combined with threading), "practical *ab initio*", and "meta predictor" methods. Significantly, Ginalski has nothing to say about Applicants' claimed method (or anything similar), which falls into neither of Ginalski's categories. Thus Ginalski's conclusions of lack of success are limited to just those classes of methods that he describes. Furthermore, Ginalski is similarly silent on the problem of predicting structures of G-Protein coupled receptors (GPCR's), as recited in Applicants' claims. However, even if specific proteins referenced by Ginalski are GPCR's, the mere fact that the methods reported by Ginalski are inadequate to predict such structures does not support a conclusion that Applicants' claimed methods are not enabled for such structures.

Second, the Examiner cites Standley *et al., PROTEINS: Structure, Function, and Genetics*, 33:240 – 252 (1998) (hereinafter, "Standley") in further support of alleged uncertainty of predictive models. Applicants assert that Standley is not dispositive for at least two reasons: first, it is dated 1998, some 2 years before Applicants' earliest priority date and therefore does not take into account any developments in the art in the intervening period. Second, Standley is limited to proteins "containing β-strands" (Standley, Abstract). Although 2 "mixed α/β proteins" are considered, a closer reading of Standley shows that it is principally focused on proteins having β-secondary structure motifs (see, *e.g.*, p. 240, right hand col. "[i]n this paper, we will be concerned with the development of models for proteins containing β-sheets"). Since Applicants' method is directed to "G-protein coupled receptors having a plurality of α helical regions", Standley is simply not relevant.

Finally, the Examiner cites Saven and Wolynes, *J. Mol. Biol.*, 257:199 – 216 (1996) (hereinafter "Saven") to show that "predicting a protein structure of an [*sic*] protein with a previously unknown structure is not a trivial task." Applicants are unclear how Saven supports the Examiner's argument. In the first instance, Saven is dated 1996, some 4 years before Applicants' earliest priority date and therefore, as with Standley, does not take into account any developments in the art in the intervening period. Second, Saven addresses a very specific aspect of the protein folding problem "local conformational tendencies ... in guiding the folding of helical proteins" (Saven, Abstract). Thus Saven, describes developing physical models used in connection with modeling mechanisms of protein folding, *i.e.*, the physical steps and pathways that take an unfolded amino acid sequence through generation of secondary structure motifs and ultimately to a folded tertiary structure. This is not germane to Applicants' claimed method, which does not model a folding process. Instead, Applicants' claimed method, hierarchically, models portions of *folded* protein structure at progressively refined levels of detail. Thus, the alleged complexity of Saven is simply not dispositive in establishing alleged unpredictability of Applicants' claimed invention.

The Examiner also alleges that, for Wands "factor d", "[t]he skill of those in art of molecular modeling and bioinformatics is high." Applicants take no position of agreement or

disagreement with the Examiner's conclusion except to say that, if taken at face value, it militates against a finding that the claimed methods require "undue experimentation" (regardless of their supposed scope), at least because whatever experimentation – if any – might be involved, those of skill in the art, being (according to the Examiner) highly skilled, would not be deterred by quite significant levels of such experimentation where necessary.

For "factor g", the Examiner alleges that the specification "provides working examples only for G-protein coupled receptors *for which the crystal structures have been fitted in the transmembrane region of the protein*." (Office Action, pages 6 – 7, emphasis herein). Applicants respectfully point out that the Examiner has mis-read the Examples section (pages 19 – 20) of Applicants' specification. It is noted that, in Example 1 (¶ [0038], page 19), it is clearly stated that the protocol described was carried out "[s]tarting from the sequence of bacteriorhodopsin, and *without using coordinates from the crystal structure*" (emphasis herein). In Example 2 (¶ [0040], page 20), it is similarly stated that the sequences of the listed olfactory receptors were used, not their structures.

Finally, the Examiner addresses "factor h" by observing that "one skilled in the art must randomly sclect parameters for 'fitting' helices and must guess what parameters to use for structure optimization" and that this would constitute "undue experimentation." Applicants respectfully disagree. Applicants note that the word "random" cannot be found in the specification of the instant application (except in reference to random access memory for a computer system) and thus question the basis of the Examiner's assertion. Nevertheless, reading the Examiner's observation in a light most favorable to her, Applicants agree that the configurations of the helices must be given an initial position. However, they are then subjected to optimization and, as one skilled in the art is well aware, optimization methods are frequently used in such instances (to find an optimal configuration starting from a less optimal starting configuration), and those methods are designed to provide an optimized structure, from many different possible starting configurations. In the instant application, Applicants actually *do* provide guidance of suitable starting configurations to one skilled in the art (see, *e.g.*, ¶ [0030], pages 13 – 14 of the specification as filed). Thus Applicants respectfully disagree that randomly

selecting parameters is an aspect of the claimed invention and, further disagree that mere choice of parameters for structure optimization does in itself constitute undue experimentation.

In summary, Applicants claimed methods, as amended herein, are directed to predicting structures for G-protein coupled receptors that comprise a plurality of α-helices, a class of proteins that the Examiner considers to be enabled by the specification of the application as filed. Accordingly, Applicants respectfully submit that the amendments and remarks herein are fully responsive to the rejection of record and request that it be removed.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the subject application is in good and proper order for allowance. Withdrawal of the Examiner's rejections and early notification to this effect are earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 839-5070.

No fee is believed owed in connection with filing of this amendment and response other than the fee associated with the petition for extension of time. However, should the Commissioner determine otherwise, the Commissioner is authorized to charge any underpayment or credit any overpayment to Fish & Richardson P.C. Deposit Account No. 06-1050 (ref. No. 06618-606001) for the appropriate amount. A copy of this sheet is attached.

Respectfully submitted,

Date: June 5th, 2007

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